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16. 03. 2004

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03007214.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

16. 03. 2004

Anmeldung Nr:
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Anmelder/Applicant(s)/Demandeur(s):

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BELGIQUE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

"Indolone-acetamide derivatives, processes for preparing them and their uses"

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17.68.EP

INDOLONE-ACETAMIDE DERIVATIVES, PROCESSES FOR PREPARING THEM AND THEIR USES

The present invention concerns indolone-acetamide derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

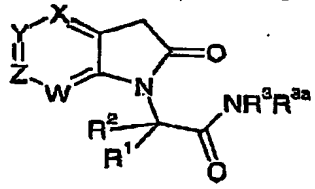
European Patent No. 0 162 036 B1 discloses the compound (S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, which is known under the International Nonproprietary Name of levetiracetam.

Levetiracetam, a laevorotary compound, is disclosed as a protective agent for the treatment and prevention of hypoxic and ischemic type aggressions of the central nervous system. This compound is also effective in the treatment of epilepsy, a therapeutic indication for which it has been demonstrated that its dextrorotatory enantiomer (R)-α-ethyl-2-oxo-1-pyrrolidine acetamide, also known from European Patent No. 0 165 919 B1, completely lacks activity (A.J. GOWER *et al.*, Eur. J. Pharmacol., 222, (1992), 193-203).

Russian patent application SU 841264 discloses 2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide and its anticonvulsant activity.

It has now surprisingly been found that certain indolone-acetamide derivatives demonstrate markedly improved therapeutic properties.

In one aspect the invention therefore provides a compound having the formula I or a pharmaceutically acceptable salt thereof.



(I)

wherein

X is N or CR^4,

Y is N or CR^5,

Z is N or CR^6,

W is N or CR^7,

R^1 is hydrogen,

R^2 is hydrogen or alkyl.

R^3 and R^{3a} both are independently selected from hydrogen, alkyl, aryl, heterocycle and alkoxy,

or NR^3R^{3a} is an heterocycle,

R^4 is hydrogen,

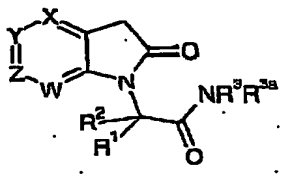
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, alkyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen and X is CR^4.

In a preferred aspect the invention therefore provides a compound having the formula I or a pharmaceutically acceptable salt thereof,



(I)

wherein

X is CR^4,

Y is CR^5,

Z is CR^6,

W is CR^7,

R^1 is hydrogen,

R^2 is hydrogen or alkyl,

R^3 and R^{3a} both are hydrogen,

R^4 is hydrogen,

R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, methyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen.

Preferably, R^2 is hydrogen, methyl or ethyl.

Preferably, R^5 is hydrogen, methyl, ethyl, trifluoromethyl, trifluoromethoxy, n-propyl, isopropyl, nitro, or halogen.

Preferably, R^6 is hydrogen, methyl or Cl.

Preferably, R^7 is hydrogen, methyl, Br, F or Cl.

More preferably, R^2 is hydrogen or methyl, R^5 is halogen or trifluoromethyl, R^6 is hydrogen and R^7 is hydrogen, Br or F.

Preferred compounds are: 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5,7-dibromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-nitro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; (2R)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; 2-[2-oxo-5-(trifluoromethoxy)-2,3-dihydro-1H-indol-1-yl]acetamide; 2-(5-isopropyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-ethyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5,7-dimethyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(2-oxo-5-propyl-2,3-dihydro-1H-indol-1-yl)acetamide; 2-[2-oxo-5-(trifluoromethyl)-2,3-dihydro-1H-indol-1-yl]acetamide; 2-(5,6-dimethyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(7-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(6-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)butanamide; (+)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)butanamide; (-)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)butanamide; 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; (+)-2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; (-)-2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; 2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; (-)-2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; (+)-2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide and 2-(5-chloro-7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide.

More preferred compounds are: 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; 2-(5,7-dibromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide; (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide; 2-[2-oxo-5-(trifluoromethyl)-2,3-dihydro-1H-indol-1-yl]acetamide and 2-(5-chloro-7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide.

In a most preferred embodiment the invention relates to a compound selected from 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide and (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-6 carbon atoms for cycloalkyl. Alkyl moieties may optionally be substituted by 1 to 5 halogen atoms. Preferred alkyl groups are methyl, ethyl, n-propyl, isopropyl and trifluoromethyl.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "nitro", as used herein, represents a group of the formula $-NO_2$.

The term "alkoxy", as used herein, represents a group of formula -OR wherein R is an alkyl group, as defined above.

The term "heterocycle", as used herein is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Non-limiting examples of aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2,4-thiadiazolyl, thieno(2,3-b)furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isoxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, 8-thia bicyclo[3.2.1]cyclooctanyl, 1,4-dithiepanyl, tetrahydro-2H-thiopyranyl, azepanyl, azocanyl, or the same which can optionally be substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, alkylidene or other groups such as halogen, hydroxy, thiol, amino, nitro, cyano, oxy derivatives, acyl derivative, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, heterocycle, vinyl, C6-10-aryl and oxo. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cycloalkyl ring, a cycloalkenyl ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2.1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

The "pharmaceutically acceptable salts" according to the invention include therapeutically active, non-toxic base salt forms which the compounds of formula I are able to form.

The compounds of formula I containing acidic protons may be converted into

their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate acid.

Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

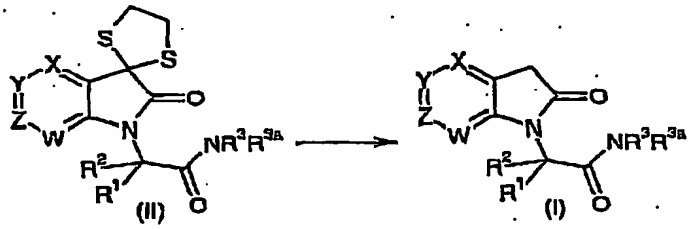
Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicity indicated in the above formula are intended to be included within the scope of the present invention.

With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

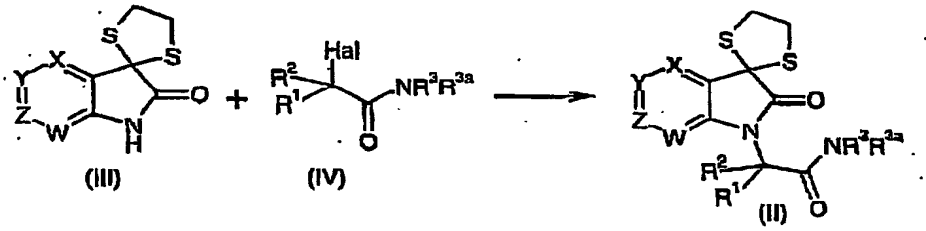
The compounds of formula I according to the invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry.

A. According to one embodiment, some compounds having the general formula I may be prepared by desulfurization of a compound of formula II according to the equation:



This reaction may be carried out using Raney nickel in an inert solvent, preferably THF, at a temperature comprised between 0 °C and 40 °C, or as described in: Mehta L., Parrick J., Payne F., J. Chem. Research (S) (1998), 190-191.

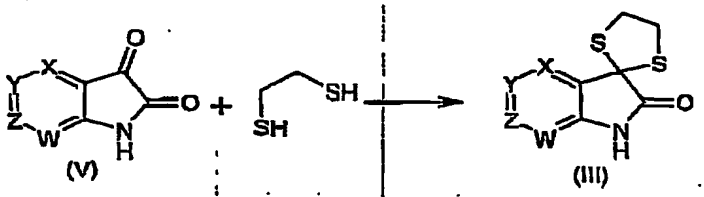
Compounds of formula II may be prepared by alkylation of a compound of formula III with a compound of formula IV according to the equation:



wherein Hal is a halogen atom, preferably Br or Cl, and X, Y, Z, W, R^1, R^2, R^3 and R^{3a} have the same definitions as described above.

This reaction may be carried out with a strong base, for example sodium hydride, at a temperature comprised between 0 and 40 °C and in an inert solvent, for example DMF under a inert atmosphere, or as described in patent GB 1,309,692 (UCB).

Compounds of formula III may be prepared by reaction of a compound of formula V with 1,2-ethanedithiol according to the equation:



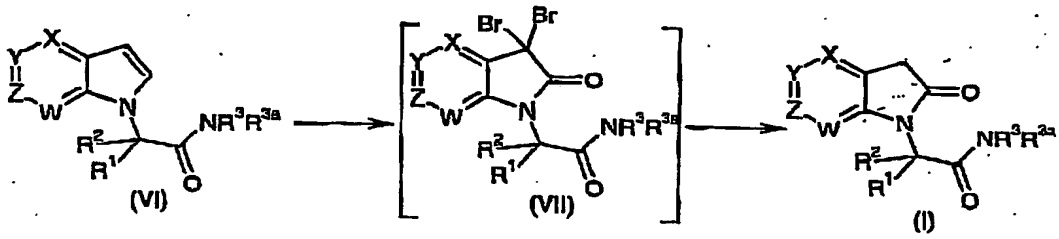
wherein X, Y, Z and W have the same definitions as described above.

This reaction may be carried out at a temperature comprised between 25 and 100 °C in an inert solvent or in acetic acid, in the presence of a Lewis acid, preferably $BF_3.Et_2O$ under an inert atmosphere.

Compounds of formula V are commercially available or may be prepared according to methods described in: Smith K., El-Hiti G.A., Hawes A.C., Synlett (1999).

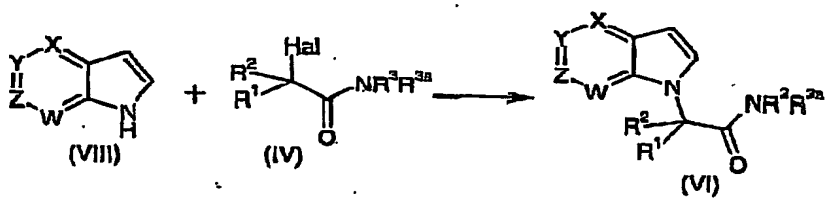
945-947; Lackey K., Sternbach D.D., Synthesis (1993), 10, 993; or Organic Synthesis, Collective Volume I, Second Edition, Gilman H. & Blatt A.H., J. Wiley & Sons Inc., 327-330.

B. According to another embodiment, some compounds having the general formula I may be prepared by bromination and oxidation of the corresponding indole of formula (VI) according to the equation:



This reaction may be carried out as described in: Marfat A., Carta M.P., Tetrahedron Lett. (1987), 28, 4027-4031.

Compounds of formula VI may be prepared by alkylation of a compound of formula VIII with a compound of formula IV according to the equation:



wherein Hal is an halogen atom, preferably Br or Cl.

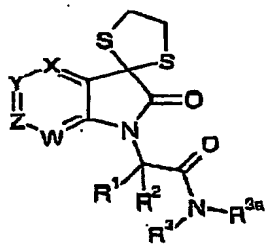
This reaction may be carried out in the presence of a strong base, preferably sodium hydride, at a temperature comprised between 0 and 40 °C, in an inert solvent, for example DMF, under a inert atmosphere, or as described in patent GB 1,309,692 (UCB).

C. According to another embodiment, some compounds having the general formula I may be prepared by halogenation of the corresponding compound of formula I wherein R^5 is an hydrogen with a N-halosuccinimide according to the procedure described in: Castanet A.-S., Colobert F., Broutin P.-E., Tetrahedron Lett. (2002), 43, 5047-5048.

According to another embodiment, some compounds having the general formula I may be prepared analogously from the corresponding compound of formula I wherein $R^5 = R^7 = H$ by using two equivalents of N-halosuccinimide.

D. According to another embodiment, some compounds having the general formula I may be prepared by nitration of the corresponding compound of formula I wherein R^5 is an hydrogen according to procedure described in: Sun L., Rubin J.R., Kraker A.J., Showalter H.D., J. Heterocyclic Chem. (1997), 34, 1399-1405.

In another embodiment, the present invention concerns also the synthesis intermediates of formula II.



(II)

wherein

X is N or CR^4,

Y is N or CR^5,

Z is N or CR^6,

W is N or CR^7,

R^1 is hydrogen,

R^2 is hydrogen or alkyl,

R^3 and R^{3a} both are independently selected from hydrogen, alkyl, aryl, heterocycle and alkoxy,

or NR^3R^{3a} is an heterocycle,

R^4 is hydrogen,

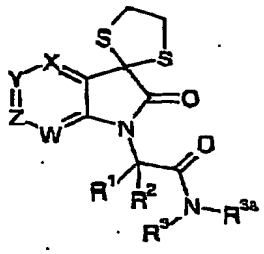
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, alkyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen and X is CR^4.

In a preferred aspect, the present invention concerns the synthesis intermediates of formula II,



(II)

wherein

X is CR^4,

Y is CR^5,

Z is CR^6,

W is CR^7,

R^1 is hydrogen,

R^2 is hydrogen or alkyl,

R^3 and R^{3a} both are hydrogen,

R^4 is hydrogen,

R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, methyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen.

Preferably, the synthesis intermediates of formula II are selected from the group consisting of:

2-(5'-methyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide,

2-[2'-oxo-5'-[(trifluoromethyl)oxy]spiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide,

2-[5'-(1-methylethyl)-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide,

2-(5'-ethyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide,

2-(5'-fluoro-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide,

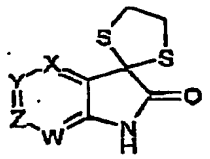
2-(5',7'-dimethyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide,

2-(2'-oxo-5'-propylspiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide,

2-[2'-oxo-5'-(trifluoromethyl)spiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide,

2-(5',6'-dimethyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide.

In another embodiment, the invention concerns also the synthesis intermediates of formula III



(III)

wherein

X is N or CR^4,

Y is N or CR^5,

Z is N or CR^6,

W is N or CR^7,

R^4 is hydrogen,

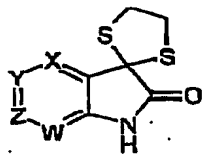
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, alkyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when X is CR^4.

In a preferred aspect, the present invention concerns the synthesis intermediates of formula III



(III)

wherein

X is CR^4,

Y is CR^5,

Z is CR^6,

W is CR^7,

R^4 is hydrogen,

R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, methyl or halogen,

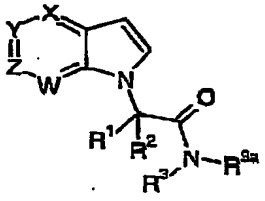
and at least one of R^5, R^6 or R^7 is different from hydrogen.

Preferably, the synthesis intermediates of formula III are selected from the group consisting of:

5'-methylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,

5'-[(trifluoromethyl)oxy]spiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5'-(1-methylethyl)spiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5'-ethylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5'-fluorospiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5',7'-dimethylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5'-propylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5'-(trifluoromethyl)spiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one,
5',6'-dimethylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one.

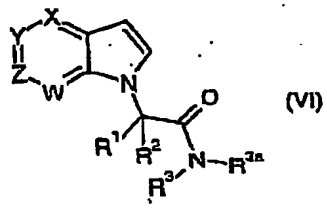
In another embodiment, the present invention concerns also the synthesis intermediates of formula VI



(VI)

wherein
X is N or CR^4,
Y is N or CR^5,
Z is N or CR^6,
W is N or CR^7,
R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are independently selected from hydrogen, alkyl, aryl, heterocycle and alkoxy,
or NR^3R^{3a} is an heterocycle,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, alkyl or halogen,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen and X is CR^4.

In a preferred aspect, the present invention concerns the synthesis intermediates of formula VI



(VI)

wherein

X is CR^4,

Y is CR^5,

Z is CR^6,

W is CR^7,

R^1 is hydrogen,

R^2 is hydrogen or alkyl,

R^3 and R^{3a} both are hydrogen,

R^4 is hydrogen,

R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, methyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen.

Preferably, the synthesis intermediates of formula VI are selected from the group consisting of :

2-(5-chloro-1H-indol-1-yl)propanamide,

2-(7-chloro-1H-indol-1-yl)acetamide,

2-(6-chloro-1H-indol-1-yl)acetamide,

2-(5-chloro-1H-indol-1-yl)butanamide,

2-(5-methyl-1H-indol-1-yl)propanamide,

2-(5-bromo-1H-indol-1-yl)propanamide,

2-(7-fluoro-1H-indol-1-yl)acetamide.

The present invention also concerns the synthesis intermediate 2-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide.

It has now been found that compounds of formula I and their pharmaceutically acceptable salts are useful in a variety of pharmaceutical disorders.

For example, the compounds according to the invention are useful for the treatment of epilepsy, epileptogenesis, seizure disorders and convulsions.

These compounds may also be used for the treatment of Parkinson's disease.

These compounds may also be used for the treatment of dyskinesia induced by dopamine replacement therapy, tardive dyskinesia induced by administration of neuroleptic drugs or Huntington Chorea.

In addition, the compounds according to the invention may also be used for treating other neurological disorders including bipolar disorders, mania, depression, anxiety, attention deficit hyperactivity disorder (ADHD), migraine, trigeminal and other neuralgia, chronic pain, neuropathic pain, cerebral ischemia, cardiac arrhythmia, myotonia, cocaine abuse, stroke, myoclonus, tremor, essential tremor, simple or complex tics, Tourette syndrome, restless leg syndrome and other movement disorders, neonatal cerebral haemorrhage, amyotrophic lateral sclerosis, spasticity and degenerative diseases, bronchial asthma, asthmatic status and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes as well as allergic and vasomotor rhinitis and rhinoconjunctivitis.

Thus, the present invention also concerns a compound having the formula I or a pharmaceutically acceptable salt thereof as defined above for use as a medicament.

In a further aspect, the present invention concerns also the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of neurological and other disorders such as mentioned above.

In particular, the present invention concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of epilepsy, Parkinson's disease, dyskinesia, migraine, bipolar disorders, chronic pain, neuropathic pain, or bronchial, asthmatic or allergic conditions.

The methods of the invention comprise administration to a mammal (preferably human) suffering from above mentioned conditions or disorders, of a compound according to the invention in an amount sufficient to alleviate or prevent the disorder or condition.

The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 5 to 1000 mg, preferably 25 to 500 mg of active ingredient per unit dosage form.

The term "treatment" as used herein includes curative treatment and prophylactic treatment.

By "curative" is meant efficacy in treating a current symtomatic episode of a disorder or condition.

By "prophylactic" is meant prevention of the occurrence or recurrence of a disorder or condition.

The term "epilepsy" as used herein refers to a disorder of brain function characterised by the periodic and unpredictable occurrence of seizures. Seizures can be "nonepileptic" when evoked in a normal brain by treatments such as electroshock or chemical convulsants or "epileptic" when evoked without evident provocation.

The term "seizure" as used herein refers to a transient alteration of behaviour due to the disordered, synchronous, and rhythmic firing of populations of brain neurones.

The term "Parkinsonian symptoms" relates to a syndrome characterised by slowness of movement (bradykinesia), rigidity and / or tremor. Parkinsonian symptoms are seen in a variety of conditions, most commonly in idiopathic parkinsonism (i.e. Parkinson's Disease) but also following treatment of schizophrenia, exposure to toxins/drugs and head injury. It is widely appreciated that the primary pathology underlying Parkinson's disease is degeneration, in the brain, of the dopaminergic projection from the substantia nigra to the striatum. This has led to the widespread use of dopamine-replacing agents (e.g. L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine agonists) as symptomatic treatments for Parkinson's disease and such treatments have been successful in increasing the quality of life of patients suffering from Parkinson's disease. However, dopamine-replacement treatments do have limitations, especially following long-term treatment. Problems can include a wearing-off of the anti-parkinsonian efficacy of the treatment and the appearance of a range of side-effects which manifest as abnormal involuntary movements, such as dyskinesias.

The term "dyskinesia" is defined as the development in a subject of abnormal involuntary movements. This appears in patients with Huntington's disease, in Parkinson's disease patients exposed to chronic dopamine replacement therapy, and in Schizophrenia patients exposed to chronic treatment with neuroleptics. Dyskinesias, as a whole, are characterised by the development in a subject of abnormal involuntary movements. One way in which dyskinesias may arise is as a side effect of dopamine replacement therapy for parkinsonism or other basal ganglia-related movement disorders.

The term "migraine" as used herein means a disorder characterised by recurrent attacks of headache that vary widely in intensity, frequency, and duration. The attacks are commonly unilateral and are usually associated with anorexia, nausea, vomiting, phonophobia, and/or photophobia. In some cases they are preceded by, or associated with, neurological and mood disturbances. Migraine headache may last from 4 hours to about 72 hours. The International Headache Society (IHS, 1988) classifies migraine with aura (classical migraine) and migraine without aura (common

migraine) as the major types of migraine. Migraine with aura consists of a headache phase preceded by characteristic visual, sensory, speech, or motor symptoms. In the absence of such symptoms, the headache is called migraine without aura.

The term "bipolar disorders" as used herein refers to those disorders classified as Mood Disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TM). American Psychiatry Association, Washington, DC, 1994). Bipolar disorders are generally characterised by spontaneously triggered repeated (i.e. at least two) episodes in which the patient's hyperexcitability, activity and mood are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (mania or hypomania), and in other occasions a lowering of mood and decreased energy and activity (depression). Bipolar disorders are separated into four main categories in the DSM-IV (bipolar I disorder, bipolar II disorder, cyclothymia, and bipolar disorders not otherwise specified).

The term "manic episode", as used herein refers to a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood with signs of pressured speech and psychomotor agitation.

The term "hypomania", as used herein refers to a less extreme manic episode, with lower grade of severity.

The term "major depressive episode", as used herein refers to a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities with signs of impaired concentration and psychomotor retardation.

The term "mixed episode", as used herein refers to a period of time (lasting at least 1 week) in which the criteria are met both for a manic episode and for a major depressive episode nearly every day.

The term "chronic pain" as used herein refers to the condition gradually being recognised as a disease process distinct from acute pain. Conventionally defined as pain that persists beyond the normal time of healing, pain can also be considered chronic at the point when the individual realises that the pain is going to be a persistent part of their lives for the foreseeable future. It is likely that a majority of chronic pain syndromes involves a neuropathic component, which is usually harder to treat than acute somatic pain.

The term "neuropathic pain" as used herein refers to pain initiated by a pathological change in a nerve which signals the presence of a noxious stimulus when no such recognisable stimulus exists, giving rise to a false sensation of pain. In other words, it appears that the pain system has been turned on and cannot turn itself off.

The term "tics" refers to common and often disabling neurological disorders. They are frequently associated with behaviour difficulties, including obsessive-compulsive disorder, attention deficit hyperactivity disorder and impulse control. Tics are involuntary, sudden, rapid, repetitive, nonrhythmic stereotype movements or vocalizations. Tics are manifested in a variety of forms, with different durations and degrees of complexity. Simple motor tics are brief rapid movements that often involve only one muscle group. Complex motor tics are abrupt movements that involve either a cluster of simple movements or a more coordinated sequence of movements. Simple vocal tics include sounds such as grunting, barking, yelping, and throat clearing. Complex vocal tics include syllables, phrases, repeating other people's words and repeating one's own words.

The activity of the compounds of formula I, or their pharmaceutically acceptable salts, as anticonvulsants can be determined in the audiogenic seizures model. The objective of this test is to evaluate the anticonvulsant potential of a compound by means of audiogenic seizures induced in sound-susceptible mice, a genetic animal model with reflex seizures. In this model of primary generalised epilepsy, seizures are evoked without electrical or chemical stimulation and the seizure types are, at least in part, similar in their clinical phenomenology to seizures occurring in man (Löscher W. & Schmidt D., Epilepsy Res. (1998), 2, p. 145-181; Buchhalter J.R., Epilepsia (1993), 34, S31-S41). Results obtained with compounds of formula I are indicative of a strong pharmacological effect.

Another assay indicative of potential anticonvulsant activity is binding to levetiracetam binding site (LBS) as hereinafter described.

Activity in any of the abovementioned indications can of course be determined by carrying out suitable clinical trials in a manner known to a person skilled in the relevant art for the particular indication and/or in the design of clinical trials in general.

For treating diseases, compounds of formula I or their pharmaceutically acceptable salts may be employed at an effective daily dosage and administered in the form of a pharmaceutical composition.

Therefore, another embodiment of the present invention concerns a pharmaceutical composition comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable diluent or carrier.

To prepare a pharmaceutical composition according to the invention, one or more of the compounds of formula I or a pharmaceutically acceptable salt thereof is

intimately admixed with a pharmaceutical diluent or carrier according to conventional pharmaceutical compounding techniques known to the skilled practitioner.

Suitable diluents and carriers may take a wide variety of forms depending on the desired route of administration, e.g., oral, rectal, or parenteral.

Pharmaceutical compositions comprising compounds according to the invention can, for example, be administered orally or parenterally, i.e., intravenously, intramuscularly or subcutaneously; intrathecally.

Pharmaceutical compositions suitable for oral administration can be solids or liquids and can, for example, be in the form of tablets, pills, dragees, gelatin capsules, solutions, syrups, and the like.

To this end the active ingredient may be mixed with an inert diluent or a non-toxic pharmaceutically acceptable carrier such as starch or lactose. Optionally, these pharmaceutical compositions can also contain a binder such as microcrystalline cellulose, gum tragacanth or gelatine, a disintegrant such as alginic acid, a lubricant such as magnesium stearate, a glidant such as colloidal silicon dioxide, a sweetener such as sucrose or saccharin, or colouring agents or a flavouring agent such as peppermint or methyl salicylate.

The invention also contemplates compositions which can release the active substance in a controlled manner. Pharmaceutical compositions which can be used for parenteral administration are in conventional form such as aqueous or oily solutions or suspensions generally contained in ampoules, disposable syringes, glass or plastics vials or infusion containers.

In addition to the active ingredient, these solutions or suspensions can optionally also contain a sterile diluent such as water for injection, a physiological saline solution, oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, antibacterial agents such as benzyl alcohol, antioxidants such as ascorbic acid or sodium bisulphite, chelating agents such as ethylene diamine-tetra-acetic acid, buffers such as acetates, citrates or phosphates and agents for adjusting the osmolarity, such as sodium chloride or dextrose.

These pharmaceutical forms are prepared using methods which are routinely used by pharmacists.

The amount of active ingredient in the pharmaceutical compositions can fall within a wide range of concentrations and depends on a variety of factors such as the patient's sex, age, weight and medical condition, as well as on the method of administration. Thus the quantity of compound of formula I in compositions for oral administration is at least 0.5 % by weight and can be up to 80 % by weight with respect to the total weight of the composition.

In accordance with the invention it has also been found that the compounds of formula I or the pharmaceutically acceptable salts thereof can be administered alone or in combination with other pharmaceutically active ingredients. Non-limiting examples of such additional compounds which can be cited for use in combination with the compounds according to the invention are antivirals, antispastics (e.g. baclofen), antiemetics, antimanic mood stabilizing agents, analgesics (e.g. aspirin, ibuprofen, paracetamol), narcotic analgesics, topical anesthetics, opioid analgesics, lithium salts, antidepressants (e.g. mianserin, fluoxetine, trazodone), tricyclic antidepressants (e.g. imipramine, desipramine), anticonvulsants (e.g. valproic acid, carbamazepine, phenytoin), antipsychotics (e.g. risperidone, haloperidol), neuroleptics, benzodiazepines (e.g. diazepam, clonazepam), phenothiazines (e.g. chlorpromazine), calcium channel blockers, amphetamine, clonidine, lidocaine, mexiletine, capsaicin, caffeine, quetiapine, serotonin antagonists, β-blockers, antiarrhythmics, triptans, ergot derivatives.

Of particular interest in accordance with the present invention are combinations of at least one compound of formula I or a pharmaceutically acceptable salt thereof and at least one compound inducing neural inhibition mediated by $GABA_A$ receptors. The compounds of formula I exhibit a potentiating effect on the compounds inducing neural inhibition mediated by $GABA_A$ receptors enabling, in many cases, effective treatment of conditions and disorders under reduced risk of adverse effects.

Examples of compounds inducing neural inhibition mediated by $GABA_A$ receptors include the following: benzodiazepines, barbiturates, steroids, and anticonvulsants such as valproate, vlagabatrine, tiagabine or pharmaceutical acceptable salts thereof.

Benzodiazepines include the 1,4-benzodiazepines, such as diazepam and clonazepam, and the 1,5-benzodiazepines, such as clobazam. Preferred compound is clonazepam.

Barbiturates include phenobarbital and pentobarbital. Preferred compound is phenobarbital.

Steroids include adrenocorticotropic hormones such as tetracosactide acetate, etc.

Anticonvulsants include hydantoins (phenytoin, ethotoin, etc), oxazolidines (trimethadione, etc.), succinimides (ethosuximide, etc.), phenacemides (phenacemide, acetylpheneturide, etc.), sulfonamides (sulthiame, acetoazolamide, etc.), aminobutyric acids (e.g. gamma-amino-beta-hydroxybutyric acid, etc.), sodium valproate and derivatives, carbamazepine and so on.

Preferred compounds include valproic acid, valpromide, valproate pivoxil, sodium valproate, semi-sodium valproate, divalproex, clonazepam, phenobarbital, vigabatrine, tiagabine.

For the preferred oral compositions, the daily dosage is in the range 5 to 1000 milligrams (mg) of compounds of formula I.

In compositions for parenteral administration, the quantity of compound of formula I present is at least 0.5 % by weight and can be up to 33 % by weight with respect to the total weight of the composition. For the preferred parenteral compositions, the dosage unit is in the range 5 mg to 1000 mg of compounds of formula I.

The daily dose can fall within a wide range of dosage units of compound of formula I and is generally in the range 5 to 1000 mg. However, it should be understood that the specific doses can be adapted to particular cases depending on the individual requirements, at the physician's discretion.

The LBS binding compounds provided by this invention and labelled derivatives thereof may be useful as standards and reagents in determining the ability of tested compounds (e.g., a potential pharmaceutical) to bind to the LBS receptor.

Labelled derivatives of LBS ligands provided by this invention may also be useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

The following examples are provided for illustrative purposes.

Unless specified otherwise in the examples, characterization of the compounds is performed according to the following methods:

NMR spectra are recorded on a BRUKER AC 250 Fourier Transform NMR Spectrometer fitted with an Aspect 3000 computer and a 5mm $^{1}H/^{13}C$ dual probehead or BRUKER DRX 400 FT NMR fitted with a SG Indigo^{2} computer and a 5 mm inverse geometry $^{1}H/^{13}C/^{15}N$ triple probehead. The compound is studied in DMSO-d_6 (or $CDCl_3$) solution at a probe temperature of 313 K or 300 K and at a concentration of 20 mg/ml. The instrument is locked on the deuterium signal of DMSO-d_6 (or $CDCl_3$). Chemical shifts are given in ppm downfield from TMS taken as internal standard.

HPLC analyses are performed using one of the following systems:

- an Agilent 1100 series HPLC system mounted with an INERTSIL ODS 3 C18, DP 5 µm, 250 X 4.6 mm column. The gradient ran from 100 % solvent A (acetonitrile, water, H_3PO_4 (5/95/0.001, v/v/v)) to 100 % solvent B (acetonitrile, water, H_3PO_4 (95/5/0.001, v/v/v)) in 6 min with a hold at 100 % B of 4 min. The flow rate is set at 2.5 ml/min. The chromatography is carried out at 35°C.

- a HP 1090 series HPLC system mounted with a HPLC Waters Symetry C18, 250 X 4.6 mm column. The gradient ran from 100 % solvent A (MeOH, water, H_3PO_4 (15/85/0.001M, v/v/M)) to 100 % solvent B (MeOH, water, H_3PO_4 (85/15/0.001 M, v/v/M)) in 10 min with a hold at 100 % B of 10 min. The flow rate is set at 1 ml/min. The chromatography is carried out at 40 °C.

Mass spectrometric measurements in LC/MS mode are performed as follows:

HPLC conditions

Analyses are performed using a WATERS Alliance HPLC system mounted with an INERTSIL ODS 3, DP 5 µm, 250 X 4.6 mm column.

The gradient ran from 100 % solvent A (acetonitrile, water, TFA (10/90/0.1, v/v/v)) to 100 % solvent B (acetonitrile, water, TFA (90/10/0.1, v/v/v)) in 7 min with a hold at 100 % B of 4 min. The flow rate is set at 2.5 ml/min and a split of 1/25 is used just before API source.

MS conditions

Samples are dissolved in acetonitrile/water, 70/30, v/v at the concentration of about 250 µgr/ml. API spectra (+ or -) are performed using a FINNIGAN (San Jose, CA, USA) LCQ ion trap mass spectrometer. APCI source operated at 450 °C and the capillary heater at 160 °C. ESI source operated at 3.5 kV and the capillary heater at 210 °C.

Mass spectrometric measurements in DIP/EI mode are performed as follows: samples are vaporized by heating the probe from 50 °C to 250 °C in 5 min. EI (Electron Impact) spectra are recorded using a FINNIGAN (San Jose, CA, USA) TSQ 700 tandem quadrupole mass spectrometer. The source temperature is set at 150 °C.

Mass spectrometric measurements on a TSQ 700 tandem quadrupole mass spectrometer (Finnigan MAT, San Jose, CA, USA) in GC/MS mode are performed with a gas chromatograph model 3400 (Varian, Walnut Creek, CA, USA) fitted with a split/splitless injector and a DB-5MS fused-silica column (15 m x 0.25 mm I.D., 1 µm) from J&W Scientific (Folsom, CA, USA). Helium (purity 99.999 %) is used as carrier gas. The injector (CTC A200S autosampler) and the transfer line operate at 290 and 250 °C, respectively. Sample (1 µl) is injected in splitless mode and the oven temperature is programmed as follows: 50 °C for 5 min., increasing to 280 °C (23 °C/min) and holding for 10 min. The TSQ 700 spectrometer operates in electron impact (EI) or chemical ionization (CI/CH_4) mode (mass range 33 - 800, scan time 1.00 sec). The source temperature is set at 150 °C.

Specific rotation is recorded on a Perkin-Elmer 341 polarimeter. The angle of rotation is recorded at 25 °C on 1 % solutions in MeOH. For some molecules, the solvent is CH_2Cl_2 or DMSO, due to solubility problems.

Melting points are determined on a Büchi 535 or 545 Tottoli-type fusionometre, and are not corrected, or by the onset temperature on a Perkin Elmer DSC 7.

Preparative chromatographic separations are performed on silicagel 60 Merck, particle size 15-40 µm, reference 1.15111.9025, using Novasep axial compression columns (80 mm i.d.), flow rates between 70 and 150 ml/min. Amount of silicagel and solvent mixtures as described in individual procedures.

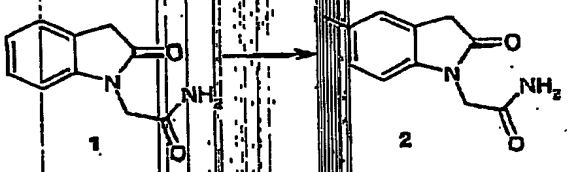
Preparative Chiral Chromatographic separations are performed on a DAICEL Chiralpak AD 20 µm, 100*500 mm column using an in-house build instrument with various mixtures of lower alcohols and C5 to C8 linear, branched or cyclic alkanes at ± 350 ml/min. Solvent mixtures as described in individual procedures.

The following abbreviations are used in the examples:

AcOEt	Ethyl acetate
CH_3CN	Acetonitrile
DMF	N,N-Dimethylformamide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

In the tables, the stereochemical information is contained in the two columns headed "configuration". The second column indicates whether a compound has no stereogenic center (achiral), is a pure enantiomer (pure), a racemate (rac) or is a mixture of two stereoisomers, possibly in unequal proportions (MIXT). The first column contains the stereochemical assignment for the recognised center, following the IUPAC numbering used in the "IUPAC name" column. A number alone indicates the existence of both configurations at that center. A number followed by 'R' or 'S' indicates the known absolute configuration at that center. A number followed by 'S' indicates the existence of only one but unknown absolute configuration at that center. The letter (A, B) in front is a way of distinguishing the various enantiomers of the same structure.

Example 1: Synthesis of 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide 2.



1 2

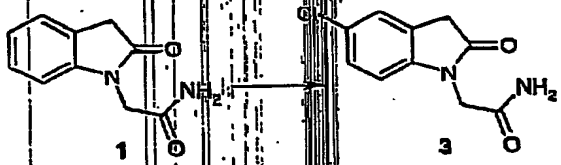
2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **1** is synthesized according to the method described by Valenta et al. (Valenta, V.; Holubeck, J.; Svatek, E.; Valchar, M.; Krejci, I.; Protiva, M.; Collect. Czech. Chem. Commun. (1990), 55, 2756-2764).

Oxindole **1** (1 g, 5.25 mmol) was dissolved in CH_3CN (20 ml). After addition of the NIS (1.3 g, 5.78 mmol), the TFA (217 µl, 1.57 mmol) was added and the reaction was allowed at room temperature for 16 h. After evaporation of the solvent, the mixture was tritured in a 10 % aqueous solution of $Na_2S_2O_3$. The beige solid formed was filtered, washed with water and with ether. After cristallization from 90 % aqueous EtOH, and re-cristallization from acetonitrile, 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **2** was obtained as a white solid.

Yield: 166 mg (10 %).

MS (GC-MS, $M^{+\cdot}$): 316.

Example 2: Synthesis of 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide 3.



1 3

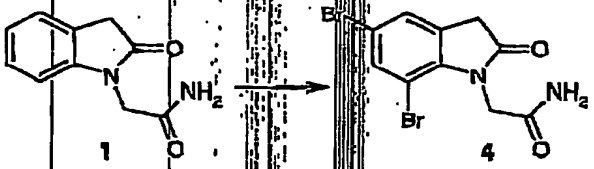
Oxindole **1** (1.77 g, 9.3 mmol) was dissolved in 90 % H_2SO_4 (6 ml) at room temperature, and NCS (1.24 g, 9.3 mmol) was slowly added with stirring. After 2 hours, the mixture was poured into cold water. The precipitate was collected, washed several times with water and then with Et_2O. After cristallization from EtOH, 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **3** was obtained as a white solid.

Yield: 479 mg (23 %).

MS (LC-MS, MH^+): 225/227.

MP: 226 °C.

Example 3: Synthesis of 2-(5,7-dibromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide 4.

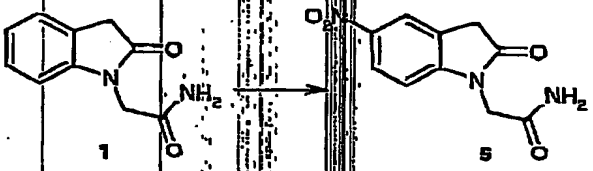


2-(5,7-dibromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **4** was obtained as described in example 1 by using 2 equivalents of NBS. The crude material was purified by silica gel chromatography (Chiralpak AD, eluent: iPrOH/Hexane 15/85).

Yield: 129 mg (10 %).

MS (LC-MS, MH^+): 259/261.

Example 4: Synthesis of 2-(5-nitro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide 5.

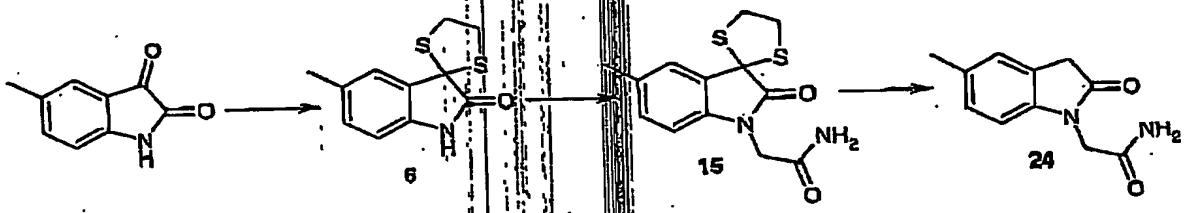


To a stirred solution of 2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **1** (400 mg, 2.1 mmol) in TFA (20 ml) was added fuming nitric acid (170 µl, 2.7 mmol) over 10 minutes. Following addition, the ice bath is removed and the mixture was stirred at room temperature for 5 minutes, then poured carefully into ice water. The precipitate was collected, washed with water until pH 7 and dried to give a crude solid. Cristallization in a mixture acetonitrile/MeOH afforded the 2-(5-nitro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **5** as a green-gray solid.

Yield: 150 mg (30 %).

MS (DIP, M^+): 235.

Example 5: Synthesis of 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide 24.



5.1 Synthesis of 5'-methylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one 6.

5-methyl-1*H*-indole-2,3-dione (6 g, 37 mmol) was suspended in 100 ml of AcOH. The heterogenous mixture was heated at 60 °C. After complete solubilisation, 1,2-ethanedithiol (3.15 ml, 37 mmol) was added and then neat $BF_3.OEt_2$ (9.5 ml, 75 mmol) was added dropwise. The reaction was stirred for 25 minutes, in which time the reaction mixture became homogenous. After 20 minutes at room temperature, the reaction was quenched by addition of water, the solid washed several times with large amount of water and air dried resulting to 5'-methylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one **6** as a brown solid.

Yield: 8.65 g (98 %).

MS (DIP, M^+): 237.

Compounds listed in table 1 can be synthesised according to the same method.

Table 1

n°	IUPAC NAME
6	5'-methylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
7	5'-[(trifluoromethyl)oxy]spiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
8	5'-(1-methylethyl)spiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
9	5'-ethylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
10	5'-fluorospiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
11	5',7'-dimethylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
12	5'-propylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
13	5'-(trifluoromethyl)spiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one
14	5',6'-dimethylspiro[1,3-dithiolane-2,3'-indol]-2'(1'H)-one

5.2 Synthesis of 2-[5'-methyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide **15**.

Compound **6** (8 g, 33.7 mmol) was dissolved in dry DMF (80 ml) under a nitrogen atmosphere. The solution was cooled at 0 °C and NaH (1.62 g, 37.13 mmol, 60 % dispersion) was carrefully added portionwise. When the nitrogen evolution ceased, bromoacetamide (5.6 g, 37.13 mmol) was added. After 30 minutes, the mixture was poured into cold water and the solid filtered off, washed with water and hexane. The crude material was directly cristallized in acetonitrile affording 2-[5'-methyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide **15** as a white solid.

Yield: 4.86 g (49 %).

MS (LC-MS, MH^+): 295.

Compounds listed in table 2 can be synthesised according to the same method.

Table 2:

n°	IUPAC NAME
15	2-(5'-methyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide
16	2-[2'-oxo-5'-[(trifluoromethyl)oxy]spiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide
17	2-[5'-(1-methylethyl)-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide
18	2-(5'-ethyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide
19	2-(5'-fluoro-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide
20	2-(5',7'-dimethyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide
21	2-(2'-oxo-5'-propylspiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide
22	2-[2'-oxo-5'-(trifluoromethyl)spiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl]acetamide
23	2-(5',6'-dimethyl-2'-oxospiro[1,3-dithiolane-2,3'-indol]-1'(2'H)-yl)acetamide

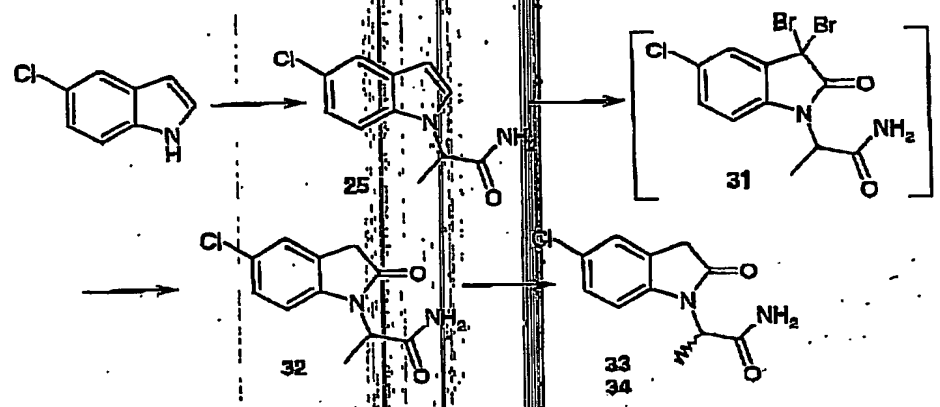
5.3 Synthesis of 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **24**.

The Raney Nickel was prepared as an aqueous slurry after removing four fifth of water of the commercial solution. Aqueous Raney nickel (10 ml) was added to a solution of compound **15** (4.06 g, 13.8 mmol) in 40 ml of distilled THF and the mixture was further vigourously stirred at room temperature. When no starting material was detected by thin layer chromatography, the mixture was diluted with THF and filtered over a Celite pad. After removal of the solvent, the crude material was purified through silica gel (CH_2Cl_2/MeOH 95/5 then 90/10), and the solvent was evaporated to yield the 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide **24** as a white solid.

Yield: 697 mg (21 %).

MS (LC-MS, MH^+): 205.

Example 6: Synthesis of 2-(5-chloro-2-oxo-2,3-dihydro-1*H*-indol-1-yl)propanamide 32, 33 and 34.



6.1 Synthesis of 2-(5-chloro-1*H*-indol-1-yl)propanamide **25**.

A dispersion of 60 % NaH (6.85 g, 0.17 mol) was added to an ice-cooled solution of 5-chloroindole (20 g, 0.13 mol) in 250 ml of dry DMF. The stirring was continued for 20 minutes at room temperature, and the mixture was cooled again with an ice bath. After portionwise addition of solid 2-bromopropanamide (24.1 g, 0.15 mol), the reaction mixture was stirred for 1h30 at room temperature, then poured into cold water and extracted 3 times with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (AcOEt/hexane 50/50) to give pure 2-(5-chloro-1*H*-indol-1-yl)propanamide **25** as a white solid.

Yield: 13.45 g (46 %).

MS (LC-MS, MH^+): 223/225.

Compounds listed in table 3 can be synthesised according to the same method.

Table 3:

n°	Configuration		IUPAC NAME
25	2	rac	2-(5-chloro-1H-indol-1-yl)propanamide
26		achiral	2-(7-chloro-1H-indol-1-yl)acetamide
27		achiral	2-(6-chloro-1H-indol-1-yl)acetamide
28	2	rac	2-(5-chloro-1H-indol-1-yl)butanamide
29	2	rac	2-(5-methyl-1H-indol-1-yl)propanamide
30	2	rac	2-(5-bromo-1H-indol-1-yl)propanamide
55		achiral	2-(7-fluoro-1H-indol-1-yl)acetamide

6.2 Synthesis of 2-(5-chloro-2-oxo-2,3-dihydro-1*H*-indol-1-yl)propanamide **32**.

Pyridinium bromide perbromide (38.8 g, 117 mmol) was added in portions over a period of 30 minutes to a stirred solution of 2-(5-chloro-1*H*-indol-1-yl)propanamide **25** (13 g, 58.4 mmol) in *tert*-butanol (100 ml) at room temperature. The reaction mixture was stirred for 30 minutes, then poured into water and diluted with AcOEt. After removal of the organic layer, the aqueous phase was extracted twice with AcOEt. Combined organic phases were dried over Na_2SO_4 and concentrated. 2-(3,3-dibromo-5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide **31** was obtained as a crude oil and was directly used in the next step, without further purification.

Zinc dust (23.71 g, 0.58 mol) was added to a stirred solution of compound **31** (theorical: 58.4 mmol) in AcOH (110 ml) at 0 °C. After 1 hour, the reaction mixture was filtered through a Celite pad. The filtrate was diluted with AcOEt and cold water. The pH was adjusted to 7 and the layers were separated. The aqueous phase was extracted again with AcOEt. Organic layers were dried over Na_2SO_4 and concentrated. The beige solid was cristallized in AcOEt and afforded 2-(5-chloro-2-oxo-2,3-dihydro-1*H*-indol-1-yl)propanamide **32** as a white solid.

Yield: 2.5 g (18 %).

MS (LC-MS, MH^+): 239/241.

Compound **32** (2.5 g, 10.5 mmol) was resolved into its enantiomers by chiral chromatography (DAICEL, Chiralcel OD phase, eluent : 50/50 ethanol/hexane) to afford enantiomers **33** (first eluted) and **34** (second eluted) as white solids.

Compound **33**:

Yield: 977 mg (39 %).

MS (LC-MS, MH^+): 239/241.

MP: 171-172 °C.

Compound **34**:

Yield: 941 mg (37 %).

MS (LC-MS, MH^+): 239/241.

MP: 171-172 °C.

Compounds described in table 4 may be prepared according to one of the previous methods.

The synthesis intermediate 2-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide may also be prepared according to one of the previous methods.

Table 4: Compounds of formula I.

n°	Configuration		IUPAC NAME	MS (LC-MS, MH^+)	α_D (MeOH, 25 °C, 1 %)
2		achiral	2-(5-Iodo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	316 (GC-MS, $M^{+\cdot}$)	
3		achiral	2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	225/227	
4		achiral	2-(5,7-dibromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	347/349/351	
5		achiral	2-(5-nitro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	235 (DIP, M^+)	
24		achiral	2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	205	
32	2	rac	2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	239/241	
33	2R	pure	(2R)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	239/241	+64.55
34	2S	pure	(2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	239/241	
35		achiral	2-[2-oxo-5-(trifluoromethoxy)-2,3-dihydro-1H-indol-1-yl]acetamide	275	
36		achiral	2-(5-isopropyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	233	
37		achiral	2-(5-ethyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	219	
38		achiral	2-(5-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	209	
39		achiral	2-(5,7-dimethyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	219	
40		achiral	2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	269/271	
41		achiral	2-(2-oxo-5-propyl-2,3-dihydro-1H-indol-1-yl)acetamide	233	
42		achiral	2-[2-oxo-5-(trifluoromethyl)-2,3-dihydro-1H-indol-1-yl]acetamide	259	
43		achiral	2-(5,6-dimethyl-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	219	
44		achiral	2-(7-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	224/226	

n°	Configuration		IUPAC NAME	MS (LC-MS, MH^+)	α_D (MeOH, 25 °C, 1 %)
45		achiral	2-(6-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	225/227	
46	2	rac	2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)butanamide	252/254	
47	A-2§	pure	(+)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)butanamide	252/254	+46.23
48	B-2§	pure	(-)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)butanamide	252/254	-38.68
49	2	rac	2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	219	
50	A-2§	pure	(+)-2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	219	+64.39
51	B-2§	pure	(-)-2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	219	
52	2	rac	2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	283/285	
53	A-2§	pure	(-)-2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	283/285	-40.38
54	B-2§	pure	(+)-2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide	283/285	+44.16
57		achiral	2-(5-chloro-7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide	243/245	

Example 7: LBS Binding Assay.

[LBS stands for Levetiracetam Binding Site cf. M. Noyer et al., Eur. J. Pharmacol. (1995), 286, 137-146.]

The inhibition constant (K_i) of a compound is determined in competitive binding experiments by measuring the binding of a single concentration of a radioactive ligand at equilibrium with various concentrations of the unlabeled test substance. The concentration of the test substance inhibiting 50 % of the specific binding of the radioligand is called the IC_{50}. The equilibrium dissociation constant K_i is proportional to the IC_{50} and is calculated using the equation of Cheng and Prusoff (Cheng Y. et al., Biochem. Pharmacol. (1972), 22, 3099-3108).

The concentration range usually encompasses 6 log units with variable steps (0.3 to 0.5 log). Assays are performed in mono- or duplicate, each K_i determination is performed on two different samples of test substance.

Cerebral cortex from 200-250g male Sprague-Dawley rats are homogenised using a Potter S homogeniser (10 strokes at 1 000 rpm; Braun, Germany) in 20 mmol/l Tris-HCl (pH 7.4), 250 mmol/l sucrose (buffer A); all operations are performed at 4 °C. The homogenate is centrifuged at 30,000g for 15 min. The crude membrane pellet obtained is resuspended in 50 mmol/l Tris-HCl (pH 7.4), (buffer B) and incubated 15 min at 37 °C, centrifuged at 30,000xg for 15 min and washed twice with the same buffer. The final pellet is resuspended in buffer A at a protein concentration ranging from 15 to 25 mg/ml and stored in liquid nitrogen.

Membranes (150-200 µg of protein / assay) are incubated at 4 °C for 120 min in 0.5 ml of a 50 mmol/l Tris-HCl buffer (pH 7.4) containing 2 mmol/l $MgCl_2$, 1 to 2 10^{-9} mol/l of [^{3}H]-2-[4-(3-azidophenyl)-2-oxo-1-pyrrolidinyl]butanamide and increasing concentrations of the test substance. The non specific binding (NSB) is defined as the residual binding observed in the presence of a concentration of reference substance (e.g. 10^{-3} mol/l levetiracetam) that binds essentially all the receptors. Membrane-bound and free radioligands are separated by rapid filtration through glass fiber filters (equivalent to Whatman GF/C or GF/B, VEL, Belgium) pre-soaked in 0.1 % polyethyleneimine and 10^{-3} mol/l levetiracetam to reduce non specific binding. Samples and filters are rinsed by at least 6 ml of 50 mmol/l Tris-HCl (pH 7.4) buffer. The entire filtration procedure does not exceed 10 seconds per sample. The radioactivity trapped onto the filters is counted by liquid scintillation in a β-counter (Tri-Carb 1900 or TopCount 9206, Camberra Packard, Belgium, or any other equivalent counter). Data analysis is performed by a computerized non linear curve fitting method using a set of equations describing several binding models assuming populations of independent non-interacting receptors, which obey to the law of mass.

Example 8: Animal model of sound-susceptible mice.

The objective of this test is to evaluate the anticonvulsant potency of a compound in sound-susceptible mice, a genetic animal model with reflex seizures. In this model of primary generalised epilepsy, seizures are evoked without electrical or chemical stimulation and the seizure types are, at least in part, similar in their clinical phenomenology to seizures occurring in man (Loscher W. & Schmidt D., Epilepsy Res. (1998), 2, 145-181; Buchhalter J.R., Epilepsia (1993), 34, S31-S41).

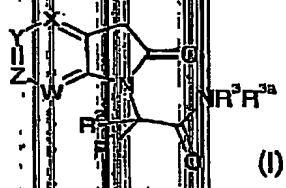
Male or female genetically sound-sensitive mice (14-28 g; N=10), derived from a DBA strain originally selected by Dr. Lehmann of the Laboratory of Acoustic Physiology (Paris) and bred in the UCB Pharma Sector husbandry unit since 1978, are used. The experimental design consisted of several groups, one group receiving the vehicle control and the other groups different doses of the test-compound. The compounds are administered intraperitoneally 60 minutes before the induction of audiogenic seizures. The range of the doses administered had a logarithmic progression, generally between 1.0×10^{-5} mol/kg and 1.0×10^{-3} mol/kg, but lower or higher doses are tested if necessary.

For testing, the animals are placed in small cages, one mouse per cage, in a sound-attenuated chamber. After a period of orientation of 30 seconds, the acoustic stimulus (90 dB, 10-20 kHz) is delivered for 30 seconds via loudspeakers positioned above each cage. During this interval, the mice are observed and the presence of the 3 phases of the seizure activity namely wild running, clonic and tonic convulsions, is recorded. The proportion of mice protected against wild running, clonic and tonic convulsions, respectively, is calculated.

For active compounds, an ED_{50} value, i.e. the dose producing 50 % protection relative to the control group, together with 95 % confidence limits, was calculated using a Probit Analysis (SAS/STAT® Software, version 6.09, PROBIT procedure) of the proportions of protected mice for each of the 3 phases of the seizure activity.

Claims

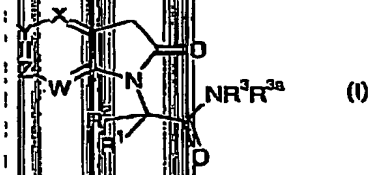
1. A compound having the formula I or a pharmaceutically acceptable salt thereof.



(I)

wherein
X is N or CR^4,
Y is N or CR^5,
Z is N or CR^6,
W is N or CR^7,
R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are independently selected from hydrogen, alkyl, aryl, heterocycle and alkoxy,
or NR^3R^{3a} is an heterocycle,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, alkyl or halogen,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen and X is CR^4.

2. A compound having the formula I or a pharmaceutically acceptable salt thereof.



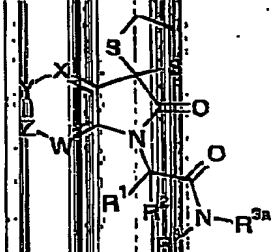
(I)

wherein
X is CR^4,
Y is CR^5,
Z is CR^6,
W is CR^7,

R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are hydrogen,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen.
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, methyl or halogen,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen.

3. A compound selected from 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)acetamide and (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide.

4. A compound having the formula II

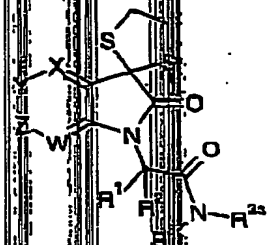


(II)

wherein
X is N or CR^4,
Y is N or CR^5,
Z is N or CR^6,
W is N or CR^7,
R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are independently selected from hydrogen, alkyl, aryl, heterocycle and alkoxy,
or NR^3R^{3a} is an heterocycle,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, alkyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen and X is CR^4.

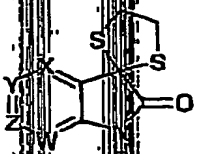
5. A compound having the formula II,



(II)

wherein
X is CR^4,
Y is CR^5,
Z is CR^6,
W is CR^7,
R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are hydrogen,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, methyl or halogen,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen.

6. A compound having the formula III,



(III)

wherein
X is N or CR^4,
Y is N or CR^5,
Z is N or CR^6,

W is N or CR^7.

R^4 is hydrogen.

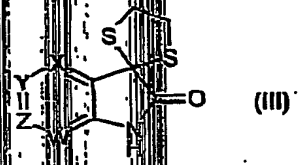
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, alkyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen when X is CR^4.

7. A compound having the formula III



(III)

wherein

X is CR^4,

Y is CR^5,

Z is CR^6,

W is CR^7,

R^4 is hydrogen,

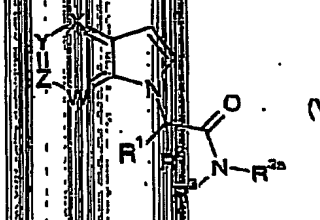
R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, alkyl or halogen,

R^7 is hydrogen, methyl or halogen,

and at least one of R^5, R^6 or R^7 is different from hydrogen.

8. A compound having the formula VI



(VI)

wherein

X is N or CR^4,

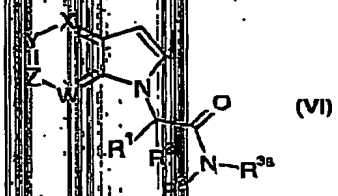
Y is N or CR^5,

Z is N or CR^6,

W is N or CR^7,

R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are independently selected from hydrogen, alkyl, aryl, heterocycle and alkoxy,
or NR^3R^{3a} is an heterocycle,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen, amino, aryl or heterocycle
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, alkyl or halogen,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen and X is CR^4.

9. A compound having the formula VI



(VI)

wherein
X is CR^4,
Y is CR^5,
Z is CR^6,
W is CR^7,
R^1 is hydrogen,
R^2 is hydrogen or alkyl,
R^3 and R^{3a} both are hydrogen,
R^4 is hydrogen,
R^5 is hydrogen, nitro, halogen, C1-3-alkyl unsubstituted or substituted by halogen, or C1-3-alkoxy unsubstituted or substituted by halogen,
R^6 is hydrogen, alkyl or halogen,
R^7 is hydrogen, methyl or halogen,
and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen.

10. A compound according to claim 1 or 2 for use as a medicament.

ABSTRACT

The present invention relates to malonic acetamide derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

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